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Breakthrough *Hormographiella aspergillata* Infections Arising in Neutropenic Patients Treated Empirically with Caspofungin▽

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***Hormographiella aspergillata*, a filamentous basidiomycete, has rarely been involved in human infections. We describe 2 febrile neutropenic patients who developed a severe pulmonary infection due to *H. aspergillata* while receiving empirical caspofungin therapy for presumed fungal pneumonia. After introduction of liposomal amphotericin B, one patient, who had neutrophil recovery, presented a favorable outcome, while the other, who remained neutropenic throughout the course of infection, died. Resistant fungi, including basidiomycetes, may emerge during empirical treatment with caspofungin in febrile neutropenic patients. A rapid switch to any other potent antifungal should be rapidly considered in case of failure of caspofungin in this setting.**

CASE REPORTS

Case description for patient 1. A 23-year-old female was diagnosed with biphenotypic acute leukemia. She received induction chemotherapy associating idarubicine, high-dose cytarabine, and corticosteroids. Because of her persistent fever while receiving large-spectrum antibiotics for febrile neutropenia, empirical caspofungin was added (70 mg on day 1, followed by 50 mg daily thereafter). Fever persisted, and she developed a dry cough and scapular pain on day 23. Serum galactomannan antigen (GMA) was repeatedly negative, and blood cultures were sterile. A chest X-ray showed an upper right lobe infiltrate, and a computed tomography (CT) scan demonstrated a nodular infiltrate surrounded by a halo sign. Caspofungin was replaced after 20 days by voriconazole (400 mg per day) for possible pulmonary aspergillosis. Despite hematological recovery and complete remission, a control CT scan on day 36 showed a progression of the lung infiltrate. A transthoracic percutaneous puncture of the lesion was performed under CT scan guidance and showed the presence of rare septated hyphae under direct microscopic examination (Fig. 1). After 13 days of voriconazole, antifungal therapy was then changed to liposomal amphotericin B starting at 5 mg/kg of body weight/day, and the patient's condition improved, with a marked reduction of the pulmonary infiltrate. Liposomal amphotericin B was then reduced to 5 mg/kg on alternate days because of severe hypokalemia. Consolidation chemotherapy was delayed for 2 weeks because of uncontrolled infection, during which time she received oral treatment with 6-mercaptopurine and etoposide. She then proceeded to the consolidation phase and received three courses of chemotherapy before undergoing myeloablative conditioning and syngeneic stem cell transplantation from her twin sister 7 months later. Hematological recovery occurred on day 15. During neutropenia, she was maintained on liposomal amphotericin at 5 mg/kg/day until day 45, when all antifungal treatment was discontinued (total duration of liposomal amphotericin B, 8 months). Three years after stem cell transplantation, she is alive and cured from her invasive fungal infection.

Case description for patient 2. A 27-year-old male with adult-onset X-linked adrenoleukodystrophy characterized by adrenal insufficiency and progressive myelopathy underwent allogeneic stem cell transplantation (allo-SCT) with unrelated cord blood following conditioning with clofarabine, busulfan, melphalan, and alemtuzumab. Graft-versus-host disease prophylaxis included cyclosporin and mycophenolate mofetil. The patient became neutropenic and febrile on day 4 and received empirical broad-spectrum antibiotics. On day 13, he became febrile again and caspofungin (70 mg on day 1, followed by 50 mg daily thereafter) was introduced in the context of *Candida albicans* fungemia. The patient remained febrile despite antibiotics and caspofungin. On day 30, pulmonary infiltrates and a splenic nodule were noticed on the CT scan. Clindamycin was added because of positive blood cultures with coagulase-negative *Staphylococcus*. GMA and *Aspergillus fumigatus*-spe-

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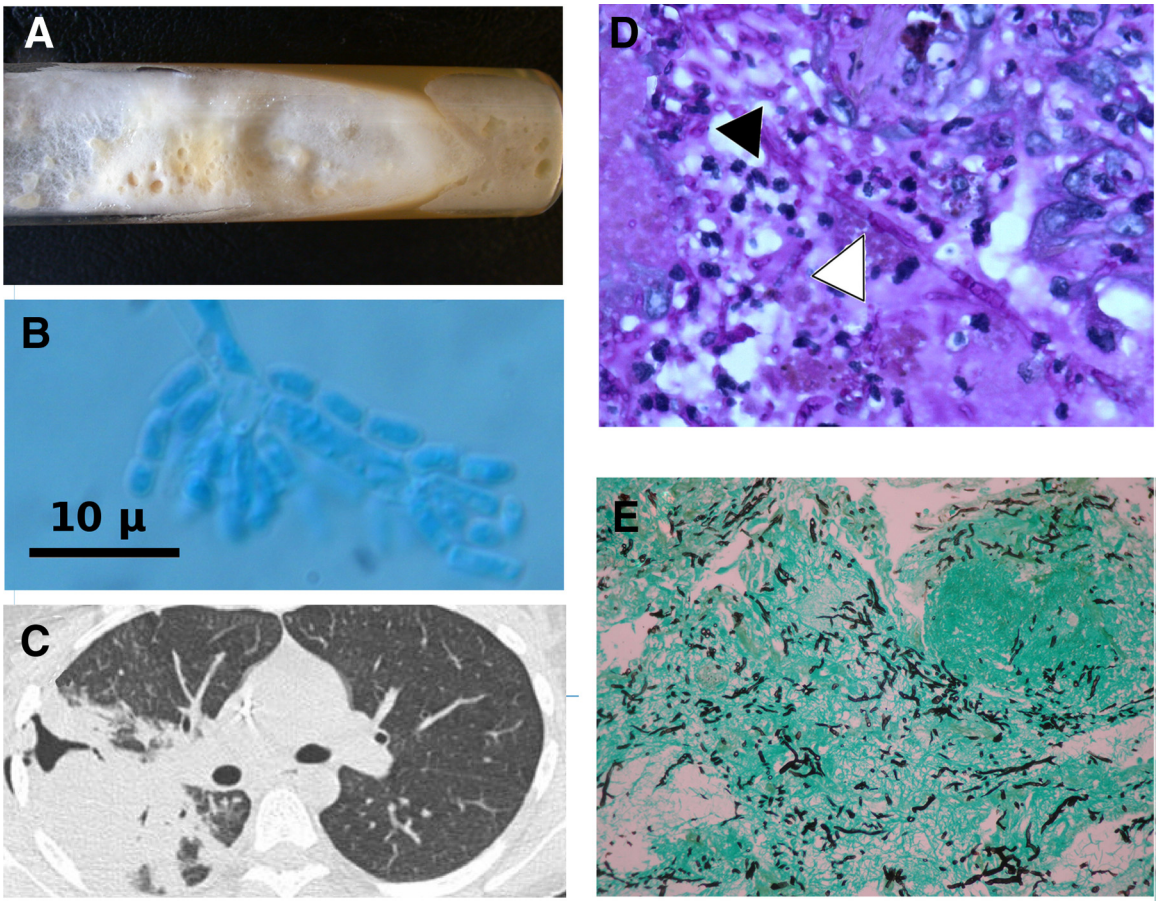

FIG. 1. (A) *H. aspergillata* cultured from lung biopsy specimen (patient 2) after 2 weeks of incubation on Sabouraud agar. (B) Morphological features of *H. aspergillata* in culture (patient 1), showing septate conidiophores bearing conidiogenous hyphae disarticulating into rectangular and round-ended arthroconidia (3 to 4 μm). (C) CT scan (patient 1) showing a lung infiltrate. (D) Periodic acid-Schiff stain of lung biopsy specimen (patient 2) that shows septated (white arrowhead) and branched (black arrowhead) hyphae (magnification, ×400). (E) Gomori-Grocott stain of lung biopsy specimen (patient 1) showing septated and branched hyphae (magnification, ×100).

cific quantitative PCR (qPCR) (27) were negative for repeated serum samples. Despite persistent fever, antifungal treatment was not changed to amphotericin B or voriconazole because of severe hypokalemia and abnormal liver function tests. On day 40, a lung CT scan showed a worsening of the nodular infiltrates. Because of delayed hematological recovery, bone marrow aspiration was performed and showed reactive histiocytosis with hemophagocytosis. Intravenous immunoglobulins were administered, and liposomal amphotericin B (3 mg/kg/day) was started (caspofungin was stopped after 27 days). The patient was transferred to the intensive care unit for mechanical ventilation. Bronchoalveolar lavage yielded only *Candida glabrata*. Blood cultures were negative, as were Epstein-Barr virus (EBV) and cytomegalovirus (CMV) PCR. The patient died on day 55 because of multiorgan failure. A postmortem lung biopsy specimen was obtained for microbiological evaluation.

Results for patient 1. A CT-guided lung biopsy specimen was homogenized and inoculated according to standard protocols for bacterial cultures and for fungal cultures on Sabouraud dextrose agar (SDA), Sabouraud dextrose agar with chloramphenicol, and Czapek medium, followed by incubation at 28°C and 37°C. Within a few days, white- to cream-colored cotton-like colonies were observed. The strain was identified at the National Reference Center for Mycoses and Antifungals, Institut Pasteur, as *Hormographiella aspergillata*, anamorph of the basidiomycete *Coprinopsis cinerea* (formerly *Coprinus cinereus*), on the basis of morphological features: septate conidiophores bearing conidiogenous hyphae disarticulating into rectangular and round-ended arthroconidia (3 to 4 μm) (Fig. 1). No fruit bodies were observed in the culture. The ITS1-5.8S-ITS2 region of the ribosomal DNA was sequenced using the universal primers V9D/LS266. The nucleotide sequence had >99% identity over 689 bp to the sexual form of *H. aspergillata* (*Coprinopsis cinerea*) compared to the published nucleotidic sequences under GenBank accession numbers AJ250588, AB097563, and AB097562. The different MICs for this isolate, determined with the EUCAST method, were quite high: amphotericin B, 2 μg/ml; 5-fluorocytosine, ≥64 μg/ml; fluconazole, 64 μg/ml; itraconazole, ≥8 μg/ml; voriconazole, 1 μg/ml; and caspofungin, 2 μg/ml.

Results for patient 2. After 4 days of incubation on Sabouraud dextrose agar with chloramphenicol and gentamicin at 35°C, a homogenized postmortem lung biopsy specimen yielded a pure culture of white- to cream-colored, cottony

TABLE 1. Previously published cases of human infections with *H. aspergillata*[a]

Gender/age (yr)	Underlying condition	Organ(s) involved by IFI	Treatment(s)	BAL	Histology (site and/or procedure)	Morphological identification (procedure)	Molecular identification of *H. aspergillata*	Outcome	Reference
F/40	ALL, relapse, auto-SCT	Lung	1, ABCD; 2, ABLC	Yes	Necrotizing fungal granuloma, septate hyphae (lung, autopsy)	*Coprinus* (BAL and autopsy); *A. flavus* (autopsy)	No	Progression under treatment; died of respiratory failure	21
M/24	ALL, allo-SCT, relapse	Lung CNS (suspected)	1, ABCD; 2, ICZ	No	Necrotizing bronchopneumonia, septate hyphae (lung, autopsy)	*H. aspergillata* (autopsy)	PCR-RFLP (ITS-1 and 2, SSU)	Progression under treatment; died of respiratory failure	29
F/34	T-cell LL	Lung	ABCD	No	No	*Coprinus* (ultrasound guided lung puncture)	PCR-RFLP (ITS1 and 2, SSU) ITS-1 sequencing	Improvement under ABCD and recovery from neutropenia; alive	28
M/34	AML, allo-SCT, relapse	Lung	CAS	Yes	Necrotizing lesion with septated hyphae (lung, autopsy)	*Coprinus* (BAL and autopsy)	ITS-2 sequencing	Progression under treatment; died of septic shock	16
F/14	AML, allo-SCT, relapse	Lung, soft palate, skin, CNS	1, VCZ; 2, PCZ; 3, PCZ + CAS; 4, ABLC + CAS	No	Fungal hyphae with sparse septation and rare branching (soft palate biopsy); skin biopsy not analyzed for histology	*Rhizomucor* (palate biopsy), *H. aspergillata* (skin biopsy)	ITS-2 sequencing	Improvement of palate (*Rhizomucor*); progression of skin (*H. aspergillata*), lung. and CNS (*H. aspergillata*?); died of respiratory failure	1
F/41	AML, allo-SCT	Lung, eyes, CNS, blood	1, VCZ; 2, PCZ; 3, CAS	Yes	IFI (in lung, eyes, CNS)	*H. aspergillata* (blood at autopsy)	LSU sequencing	Progression under treatment; died of CNS involvement	6
F/63	AML		1, VCZ; 2, PCZ; 3, VCZ	Yes	IFI (in lung biopsy)	*H. aspergillata* (lung biopsy)	LSU sequencing	Improvement of IFI under VCZ (third line); died of AML progression	6
M/44	AML, allo-SCT	Lung	1, VCZ; 2, ABLC; 3, VCZ	No	IFI (in lung biopsy)	*H. aspergillata* (lung biopsy)	LSU sequencing	IFI stable; died of severe GVHD	6

[a] M, male; F, female; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; LL, lymphoblastic lymphoma; IFI, invasive fungal infection; SCT, stem cell transplantation; GVHD, graft-versus-host disease; CNS, central nervous system; BAL, bronchoalveolar lavage; ABCD, amphotericin deoxycholate; ABLC, liposomal amphotericin B; ICZ, itraconazole; VCZ, voriconazole; PCZ, posaconazole; CAS, caspofungin; PCR-RFLP, PCR, restriction fragment length polymorphism; ITS, internal transcribed spacer region; SSU, nuclear ribosomal small subunit; LSU, nuclear ribosomal large subunit.

mold (Fig. 1). Microscopically, the mold exhibited septate hyphae with cylindrical arthroconidia. Ribosomal DNA, including the complete ITS1-5.8S-ITS2 region, was amplified with the fungal universal primer pair ITS1/ITS4, and both strands of PCR products were sequenced. Sequence comparison analysis using the GenBank database (National Center for Biotechnology Information) demonstrated ≥99% identity over 549 bp with the *Coprinopsis cinerea* sequences (GenBank accession numbers AB097562 and GU327634; ATCC no. MYA-4618; anamorph, *Hormographiella aspergillata*).

The postmortem examination of the lungs disclosed inflammatory lesions with neutrophil infiltration and necrotic granulomatous lesions with histiocytic cells, multinucleated giant cells, and many hyphae. Periodic acid-Schiff stain showed damaged hyphae with irregular staining. The hyphae were septate and branching at an acute angle (Fig. 1).

Discussion. Patients undergoing intensive chemotherapy for acute leukemia or stem cell transplantation are at an increased risk of invasive fungal infection (IFI). *Aspergillus* spp. and *Candida* spp. are the fungi most frequently involved (22). Despite major advances in diagnostic procedures and antifungal therapy in the last decade, the prognosis of IFI in the setting of hematological malignancies remains poor, with close to 50% of patients failing frontline treatment and a mortality rate in the range of 30% (12). The advent of new diagnostic tools, including serum enzyme-linked immunosorbent assay (ELISA) for GMA (18), qPCR of fungal DNA (20, 27), and computed tomography of the lungs (11), has allowed early detection of IFI and prompt treatment. In recent years, many new antifungal drugs have become available, including a liposomal formulation of amphotericin B, extended-spectrum azoles (voriconazole and posaconazole), and echinocandins (25). The latter represent a new class of antifungal drugs targeting the synthesis of β-(1,3)-D-glucan, a major component of the fungal cell wall. Caspofungin, the first drug of its class, was approved for empirical treatment in febrile neutropenic patients and for first-line therapy of systemic candidiasis and second-line therapy of invasive aspergillosis (19). It is currently the only echinocandin approved for the latter indication.

Currently, empirical treatment is still widely used in neutropenic patients who remain febrile despite large-spectrum antibacterial agents (30), because prompt treatment of IFI remains one of the major prognostic challenges (24). Liposomal formulations of amphotericin B and caspofungin are approved for empirical treatment of febrile neutropenia. The tolerance profile of caspofungin and its minor drug interactions allow its use in high-risk neutropenic patients with major comorbidities (3). However, natural or acquired resistance of some fungi remains an important issue in the setting of empirical treatment of immunocompromised patients (8, 13).

Aspergillus fumigatus remains the most common cause of IFI in patients with hematological malignancies (14). Other filamentous fungi responsible for severe infections in immunocompromised hosts include non-*fumigatus Aspergillus* species, zygomycetes, *Fusarium* spp., and *Scedosporium apiospermum* (4, 22). Basidiomycetes, including *Cryptococcus* spp., *Geotrichum* spp., and *Trichosporon* spp., are intrinsically resistant to echinocandins (7, 9) and have become increasingly recognized as clinically significant fungi in the last 20 years (15). Invasive infections with *H. aspergillata*, anamorph of *Coprinus cinereus* (10), are anecdotal. Indeed, so far, 8 cases have been described in the literature, all in patients with hematological malignancies (1, 6, 16, 21, 28, 29) (Table 1).

Although the spores of the basidiomycete *H. aspergillata* are abundantly present in the environment and the fungus grows well at 37°C, it has rarely been found in human infection, and a causal relationship has sometimes been difficult to assess. Other isolated cases of invasive infections caused by *H. aspergillata* include endophthalmitis (2), endocarditis (26), and chronic sinusitis (23).

The 2 patients described here had severe proven lung infections demonstrated both by histology and by culture of *H. aspergillata*. In both cases, infection developed and worsened under caspofungin therapy. Patient 1 survived after antifungal treatment was changed to high-dose liposomal amphotericin B despite high MICs. Furthermore, neutrophil recovery in this patient may have had a direct impact on the control of the fungal infection. She was maintained on preventive liposomal amphotericin B while undergoing allogeneic SCT with no recurrence of infection. The second patient died of progressive infection despite introduction of liposomal amphotericin B. Failure may have been due to a delayed introduction of amphotericin B, resistance to the drug, or absence of recovery from neutropenia, as in some previously reported cases (1, 29). Since caspofungin became available, it has been widely used for the treatment of suspected invasive fungal infections in neutropenic patients because of its well-documented efficacy and excellent tolerance profile. Nevertheless, emergence of yeasts and molds, with or without either primary or acquired resistance to echinocandins, is beginning to be a concern, especially in hematologic patients (5, 8; P. Sujobert, N. Boissel, A. Bergeron, P. Ribaud, H. Dombret, O. Lortholary, and E. Raffoux, submitted for publication). The susceptibility of basidiomycetes to available antifungal agents is not well known (10). MICs were available for one isolate (patient 1) and were elevated for most antifungal drugs, possibly explaining the initial failure of treatment. Amphotericin B remains the antifungal agent with the largest spectrum of activity against yeasts and filamentous fungi. Its efficacy and tolerance have been improved by the use of a liposomal formulation (17). Empirical treatment with caspofungin should therefore be strictly monitored for early recognition of failure and an early switch in case of emerging resistant yeast or mold isolates.

Nucleotide sequence accession numbers. The ITS1-5.8S-ITS2 region of the fungal ribosomal DNA from patient 1 was deposited in GenBank under accession number GQ131575. Fungal ribosomal DNA, including the complete ITS1-5.8S-ITS2 region, from patient 2 was deposited in GenBank under accession number HQ433353.

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